Rapid and Robust B Cell Depletion in Preliminary Results of a Phase 2 Study of Ublituximab, Novel Glycoengineered Anti-CD20 Mab, RMS Patients

Amy Lovett-Racke, PhD

May 26, 2017

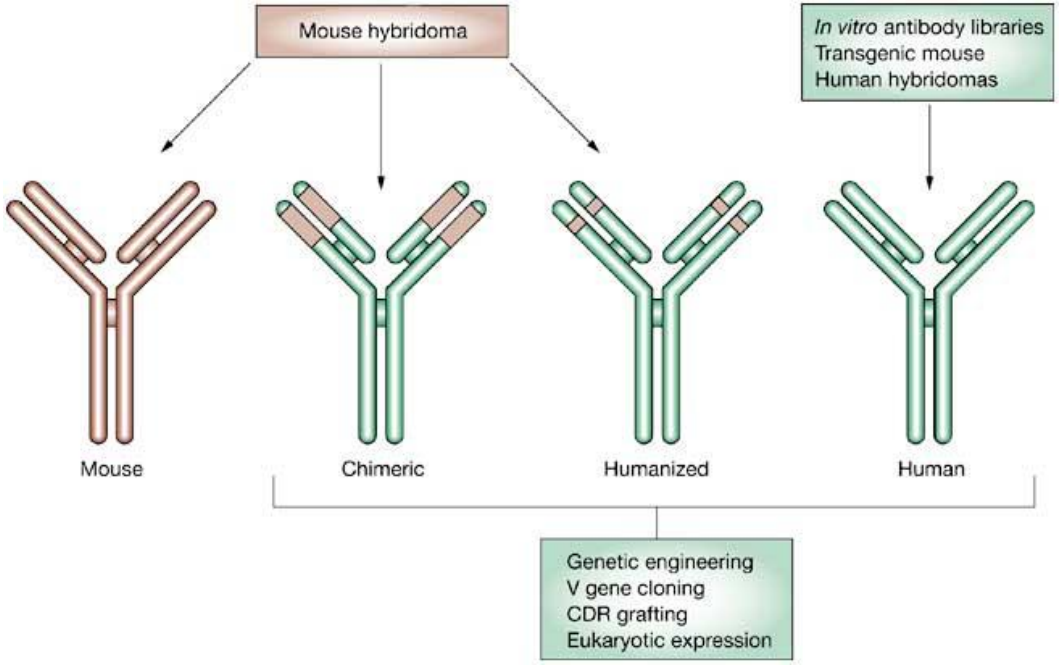
Disclosures

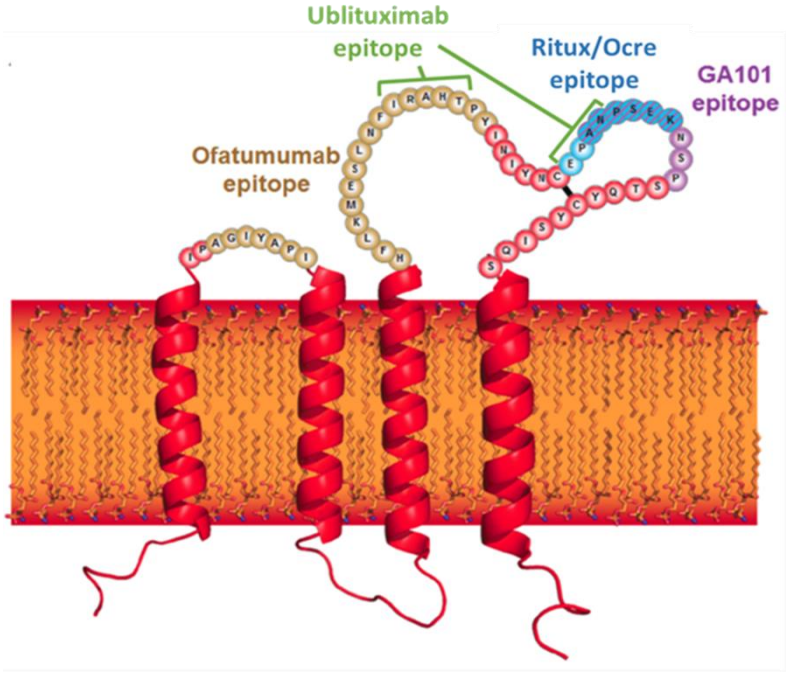
- This clinical trial and immune profile study was funded by TG Therapeutics, New York.

- Grants from these agencies support additional research in my lab.
  - National Institutes of Health
  - National Multiple Sclerosis Society
  - Strategic Pharmaceutical Academic Research Consortium

Background

- Ublituximab (TG-1101) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen, and glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab





CD20 Antibody Epitopes

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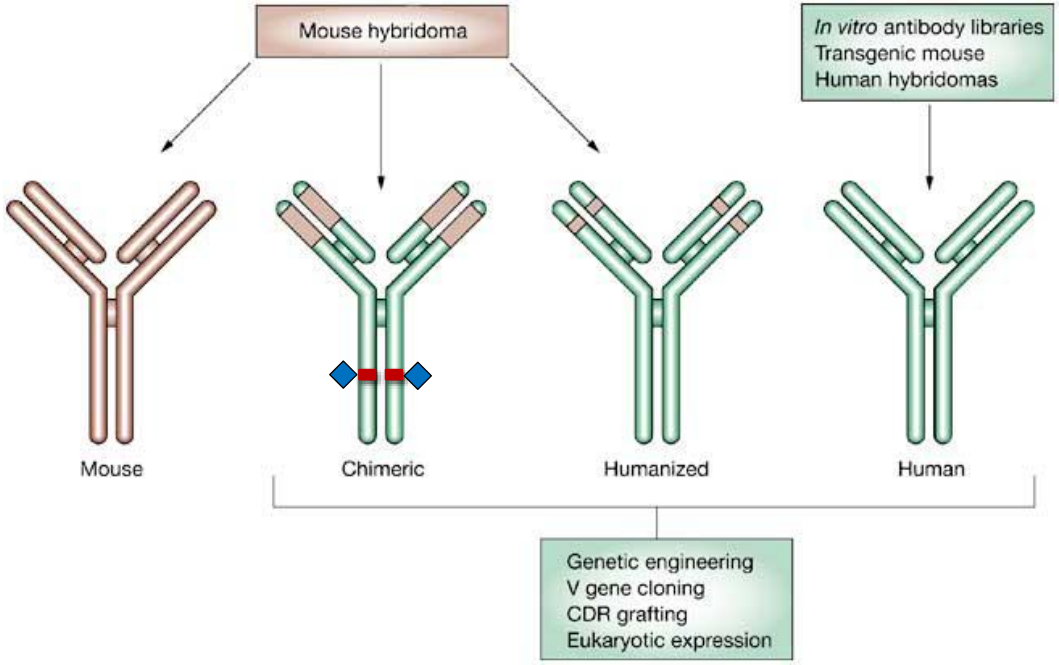

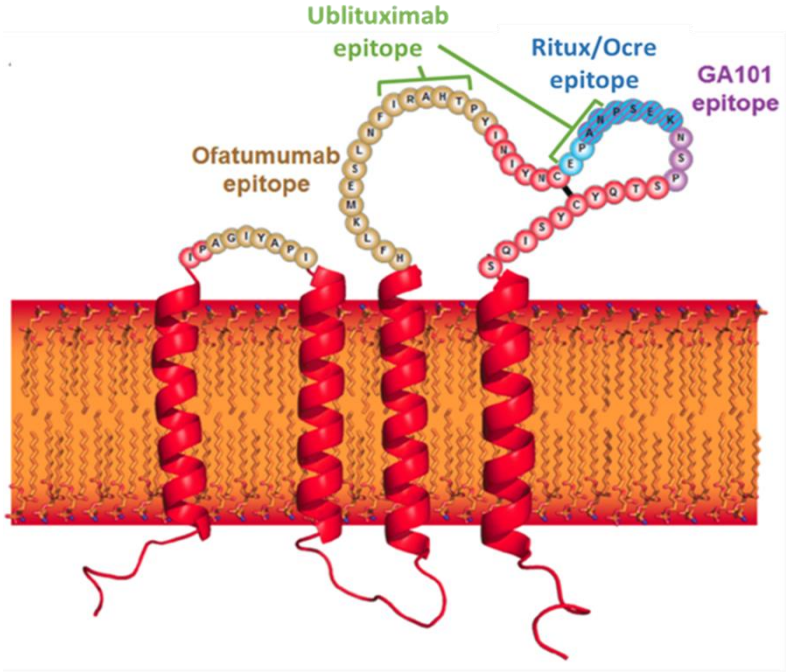

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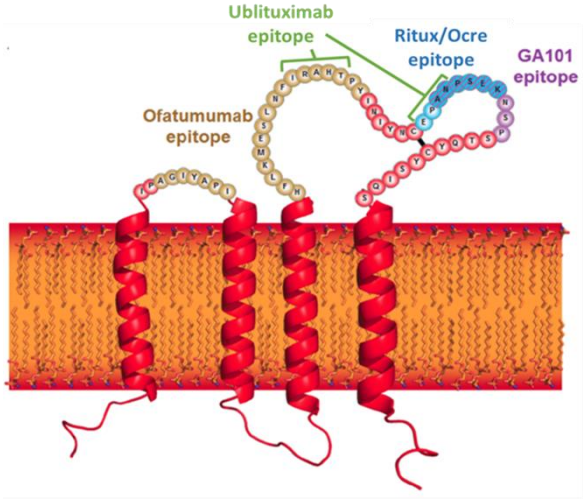

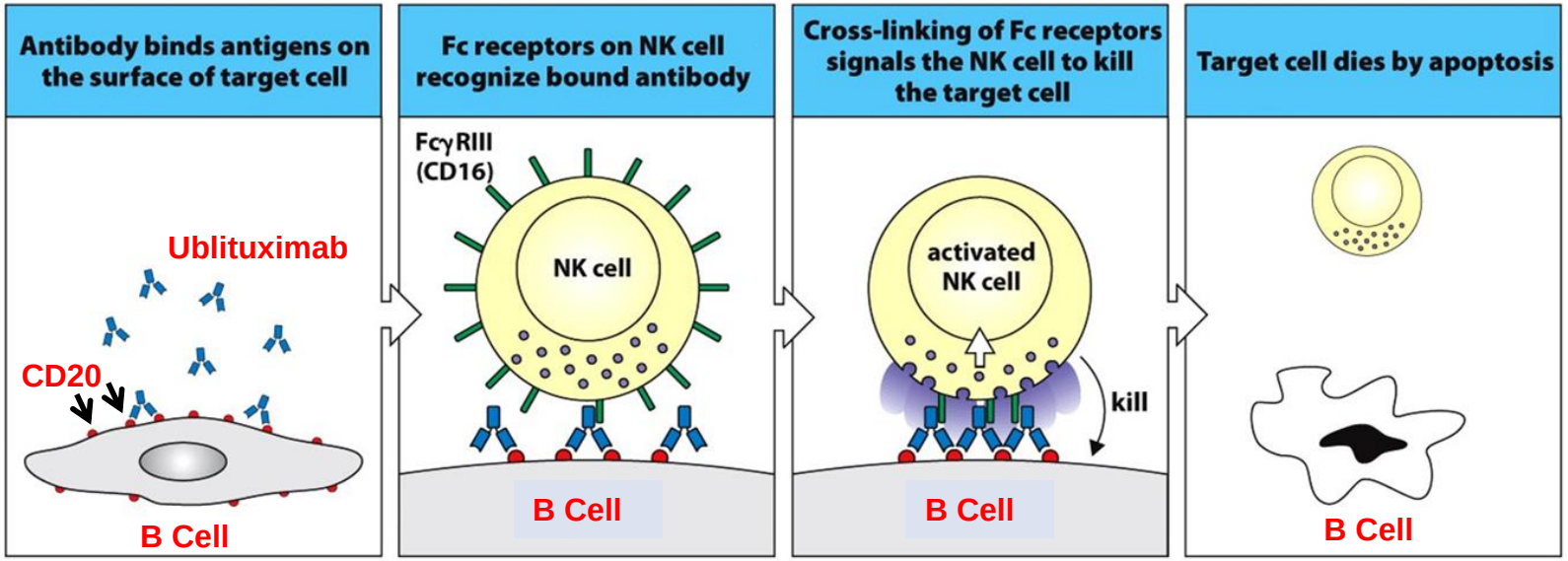

Figure 9.43 The Immune System, 3ed. (© Garland Science 2009)

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Objective

- TG1101 RMS201 (clinicaltrials.gov NCT02738775) is a randomized, placebo controlled, multi-center study to test the safety and efficacy of ublituximab, at doses markedly less than used in ongoing Phase 3 oncology studies, and at a range of infusion times, with a goal of rapid infusions

- Primary endpoint is the Responders Rate, defined as percent of subjects with ≥95% reduction in peripheral CD19+ B-cells within 2 weeks after the second infusion (day 15)

- The TG1101 RMS201 study in ongoing and will incorporate additional clinical and MRI measures (see Study Design). We report preliminary results of B cell depletion after the second infusion

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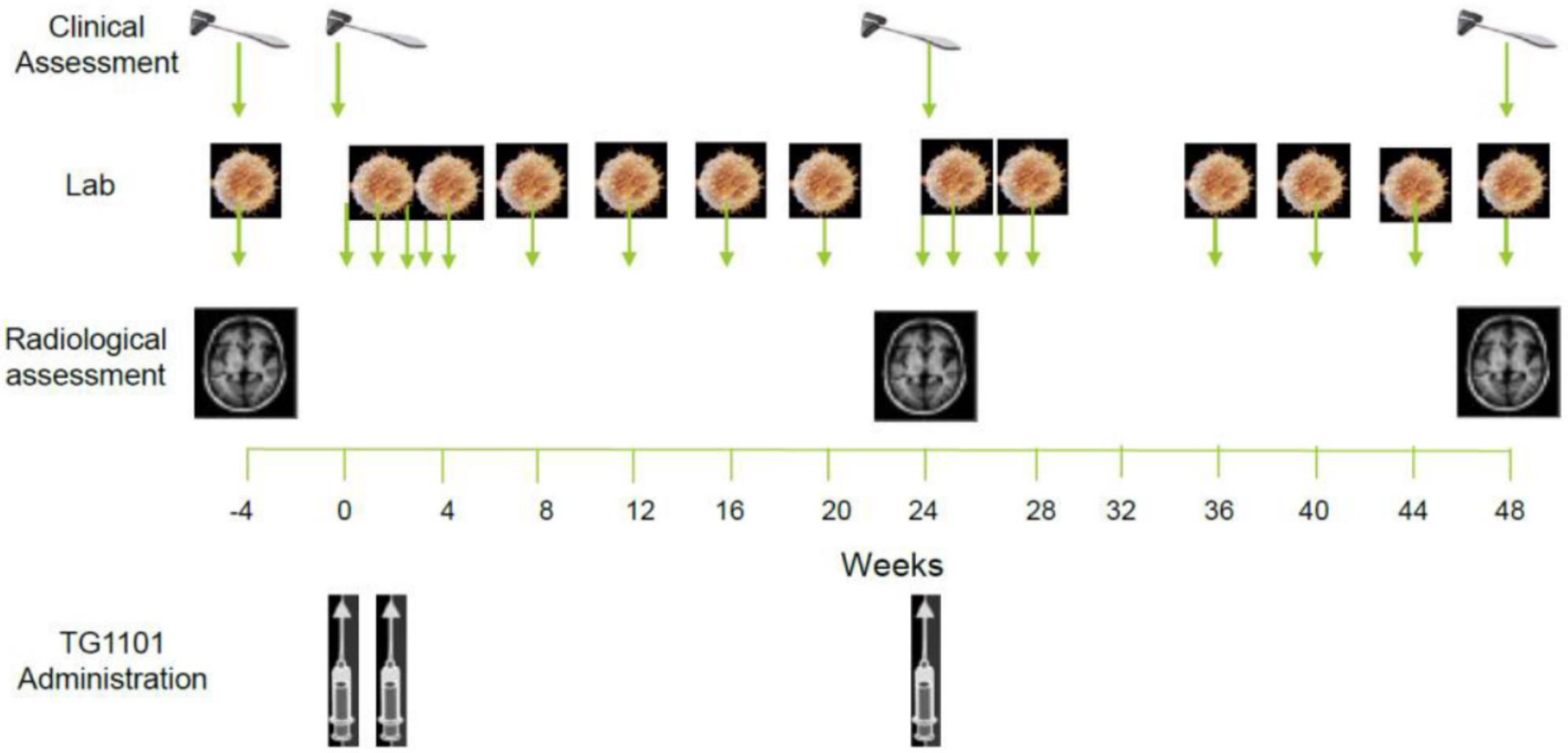
Study Design



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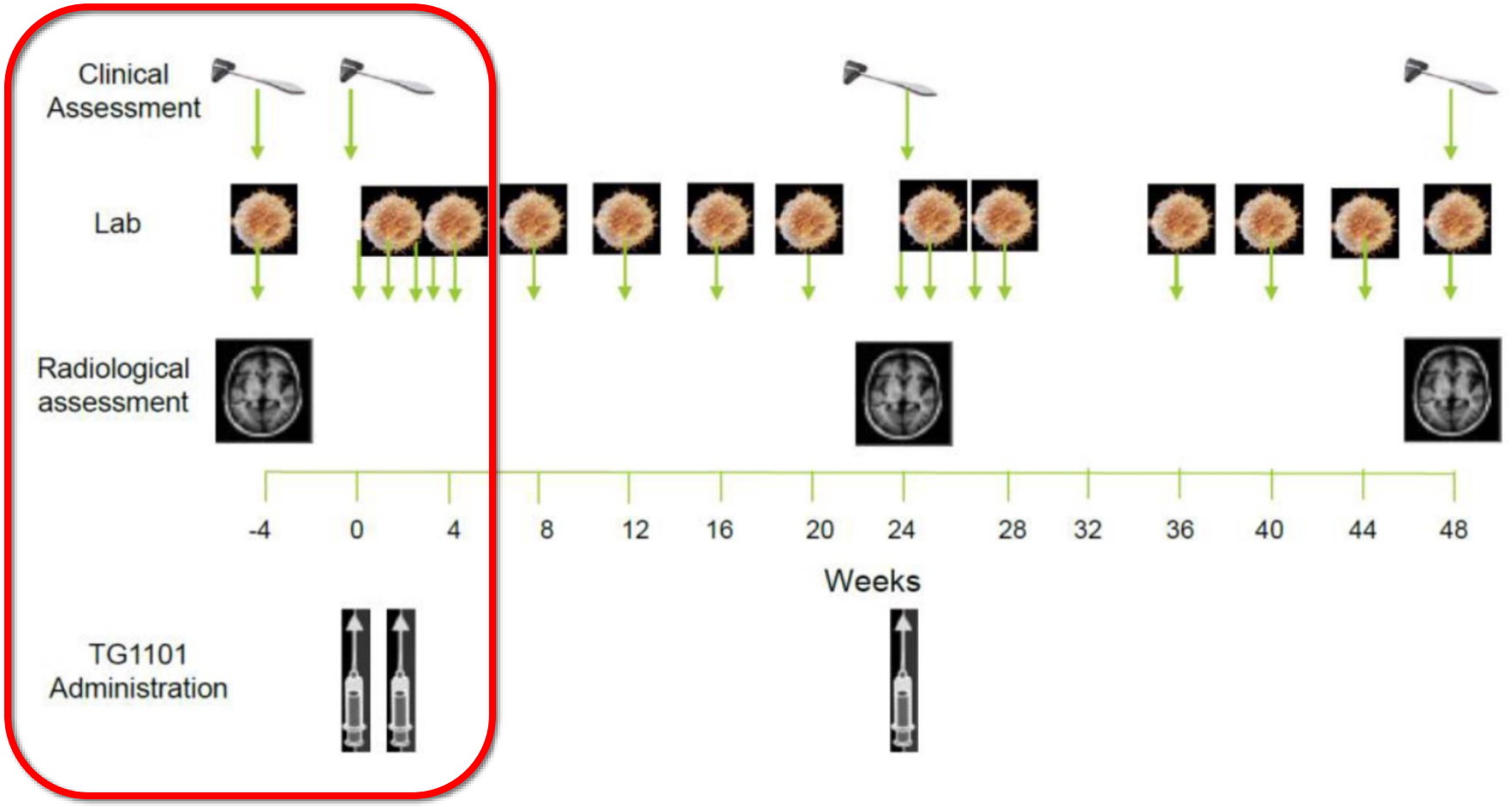
Study Design

Placebo Phase



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Study Design

Randomization		Treatment Period		
Cohort	**Subjects and treatment**	**Day 1/ infusion time**	**Day 15/ infusion time**	**Week 24/ infusion time**
1	Placebo (n=2)	Placebo / 4h	Placebo / 3h	-
	UTX (n=6)	150 mg / 4h	450 mg / 3h	450 mg / 1.5h
2	Placebo (n=2)	Placebo / 4h	Placebo / 1.5h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1.5h	450 mg / 1h
3	Placebo (n=2)	Placebo / 4h	Placebo / 1h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1h	600 mg / 1h

Three additional cohorts have been added to further reduce infusion times to 1 hr.

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Patient Demographics

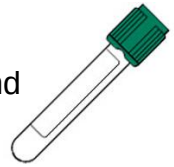
Baseline Demographics				
Cohort	**Subjects and Treatment**	**Age (Years)[1]**	**Gender (% Female)**	**Disease Duration (Years)[1,2]**
1	Placebo (n=2)	39±14	50%	15.5±20.4
	UTX (n=6)	43±12	67%	7.1±7.3
2	Placebo (n=2)	44±1	0%	0.9±1.2
	UTX (n=6)	33±10	100%	5.3±6.4
3	Placebo (n=2)	38±7	50%	11.5±7.5
	UTX (n=6)	40±11	67%	13.4±10.0
Total	**n=24**	**40±11**	**67%**	**8.8±9.0**

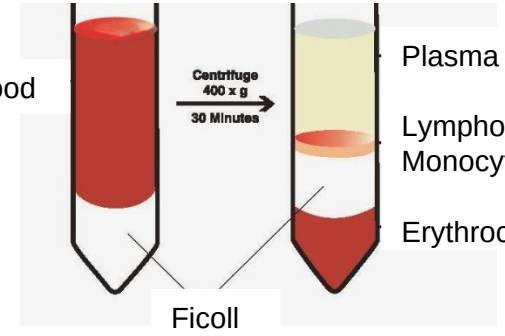
[1] Mean ± Standard Deviation

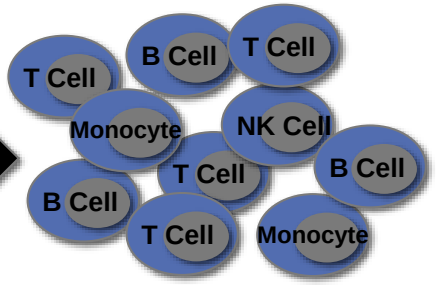
[2] Distribution of times from diagnosis: 11 subjects (45.8%) were less than 5 years, 7 (29.2%) were 5-10 years, and 6 (25%) were greater than 10 years.

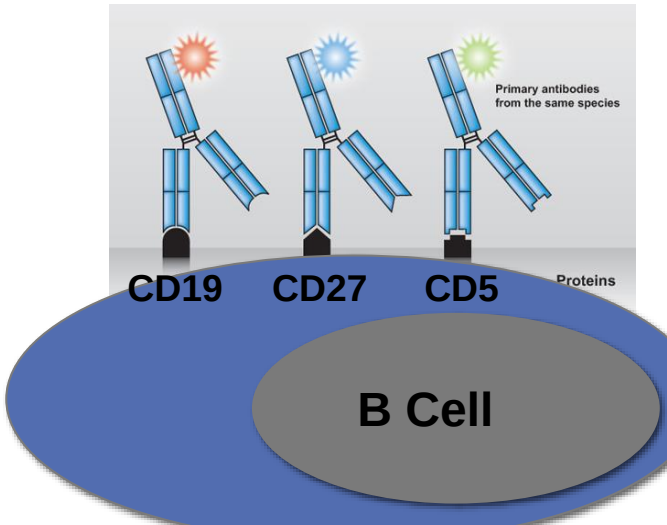
Immune Profiling

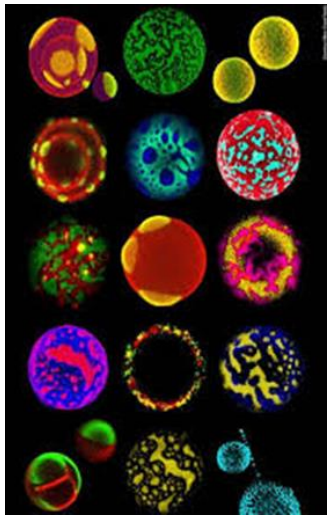
Blood is collected in heparinized tubes and shipped to OSU.

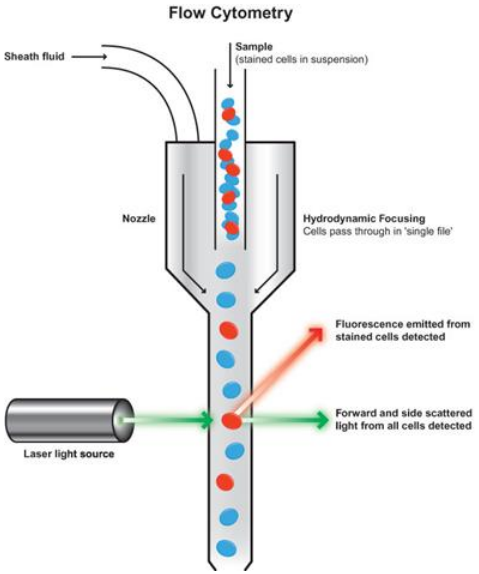












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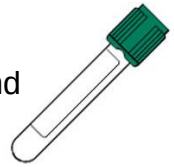

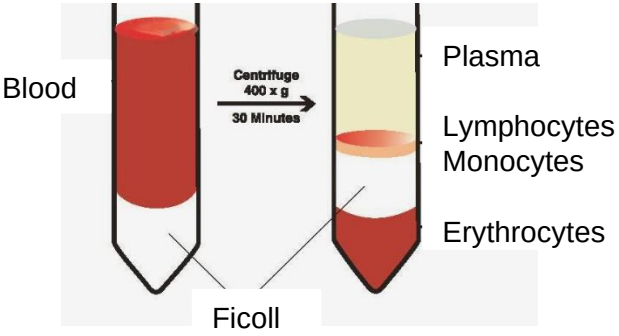

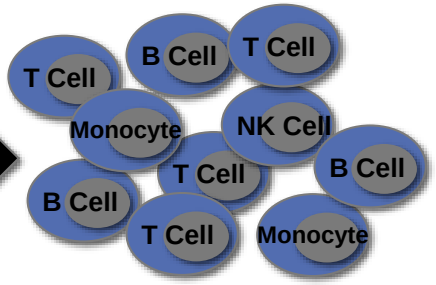

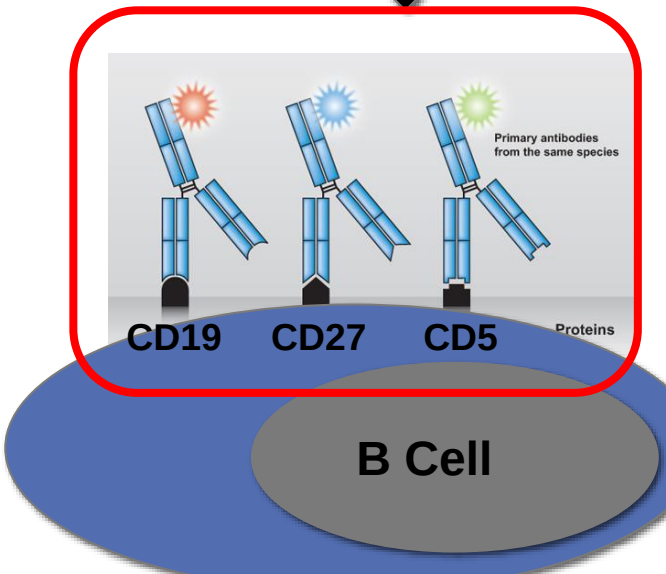

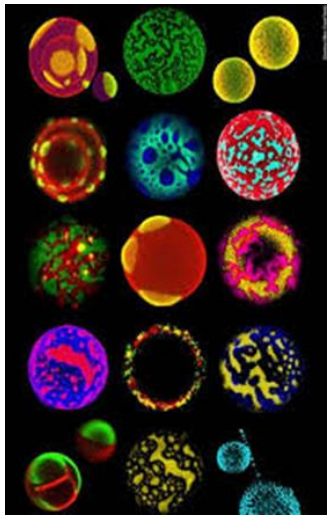

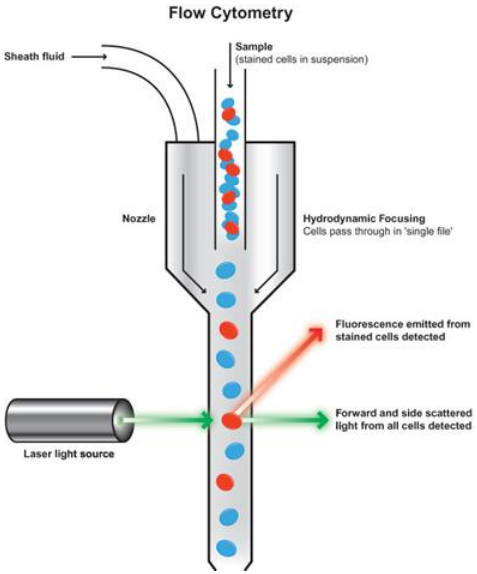

Immune Profiling

B/NK Cell Panel
CD3
CD19
CD5
CD1d
CD27
CD56
CD16

Activated/Reg B Cell Panel (PMA/Ion/CpG)
CD3
CD19
CD5
CD1d
CD27
IL-10
IL-27/35

T Cell Panel
CD3
CD4
CD8
CD45RA
CD27

Treg Cell Panel
CD3
CD4
CD25
FoxP3

Helper T Cell Panel (PMA/Ion)
CD3
CD4
CD45RA
IL-10
IFNγ
GM-CSF
IL-17

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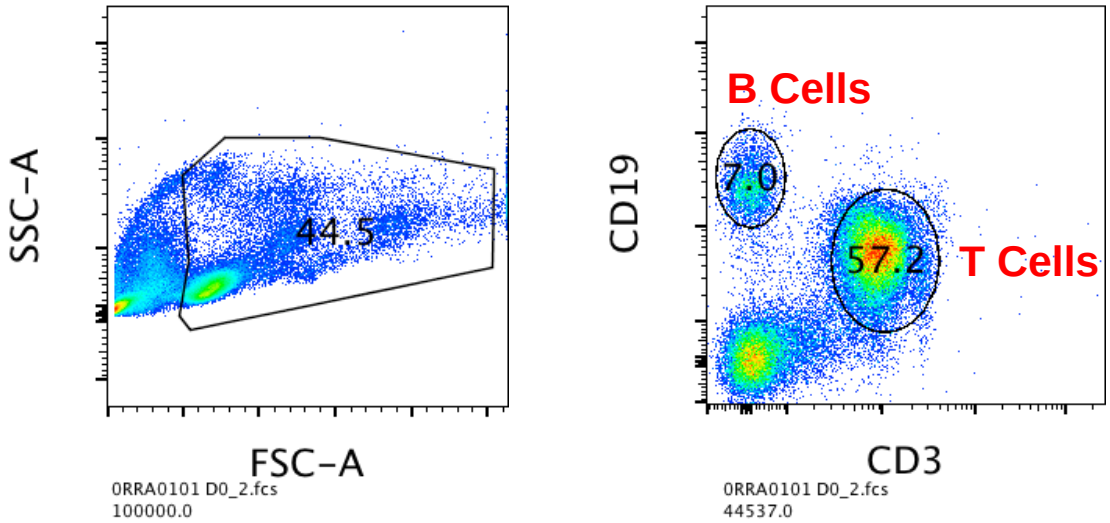
B Cell Analysis



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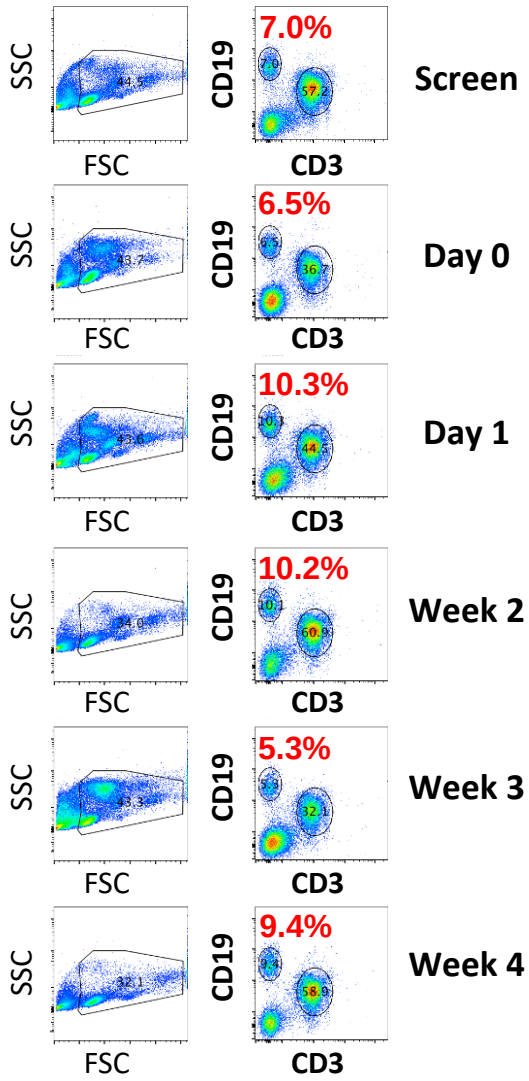
B Cell Analysis

Placebo Phase



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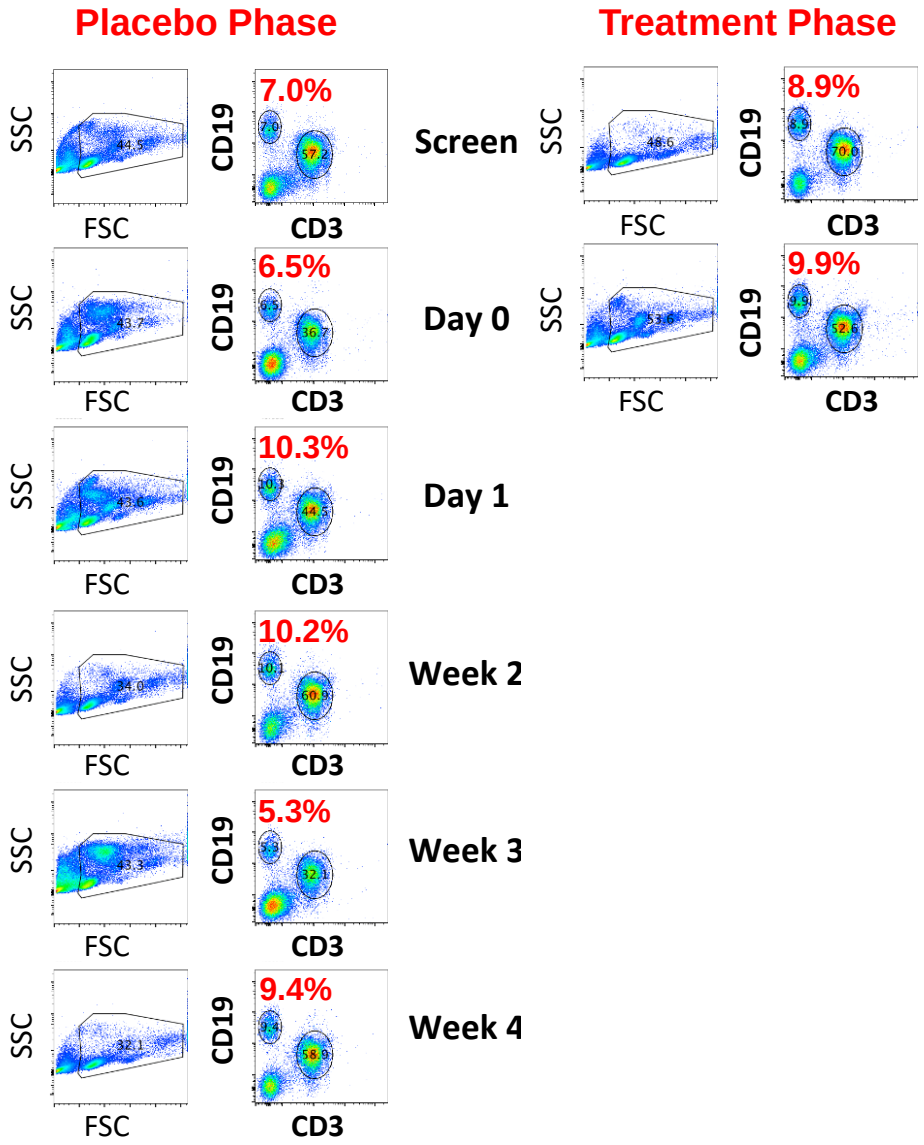

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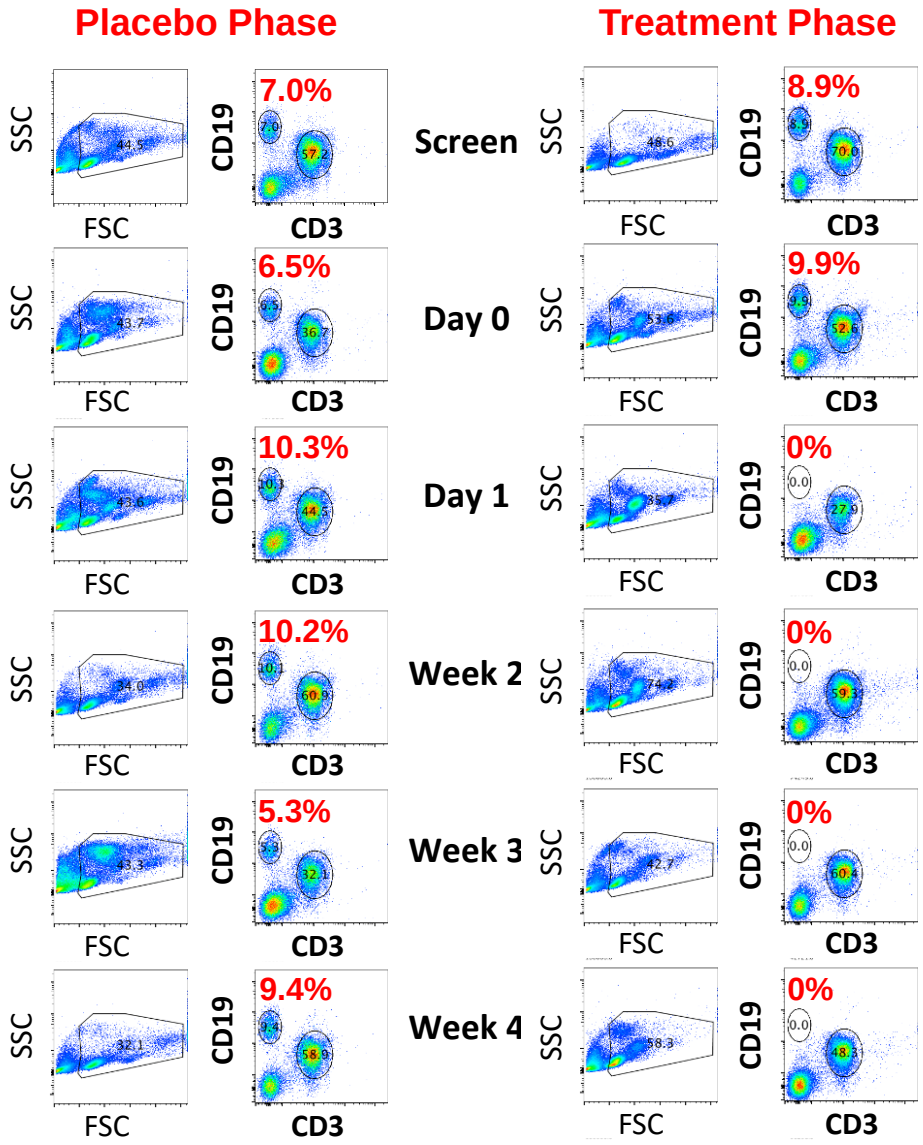

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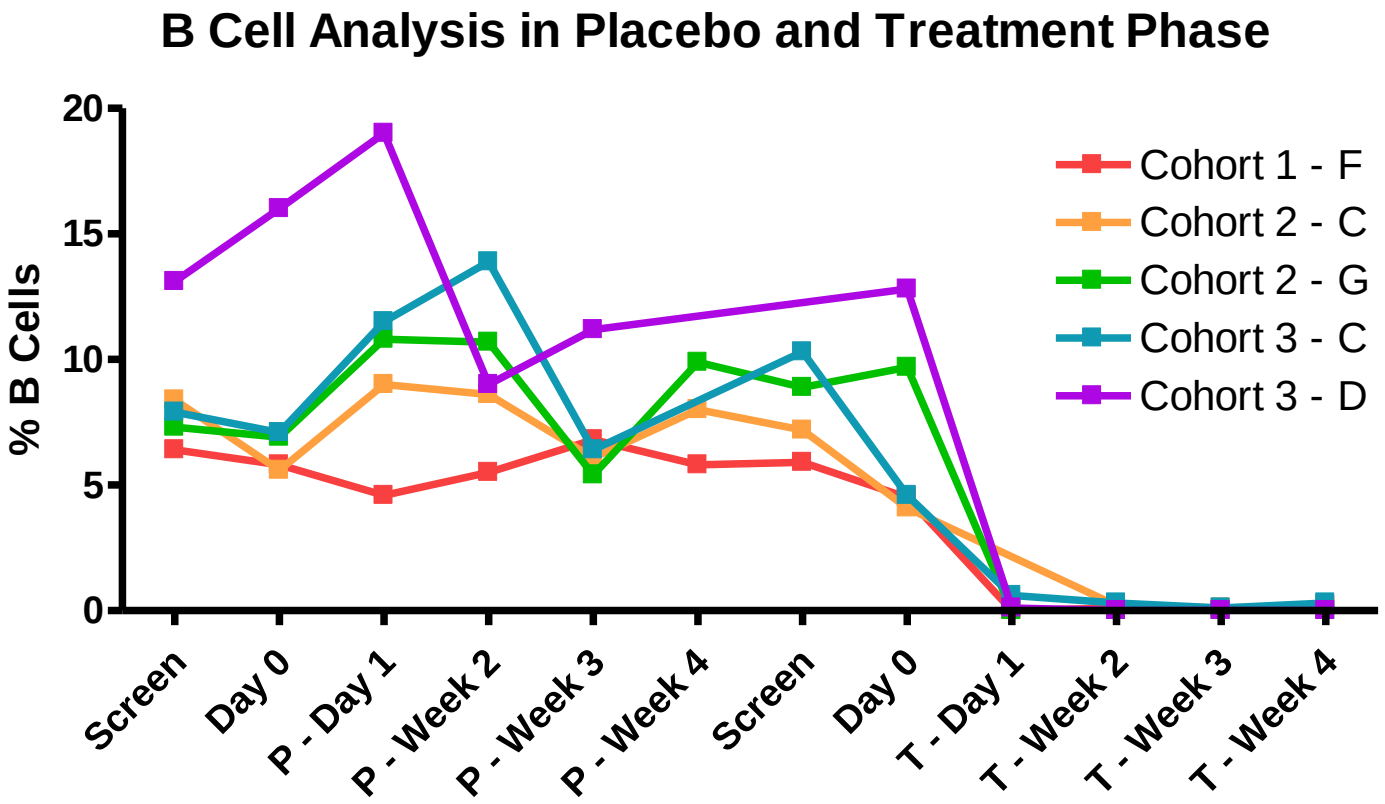

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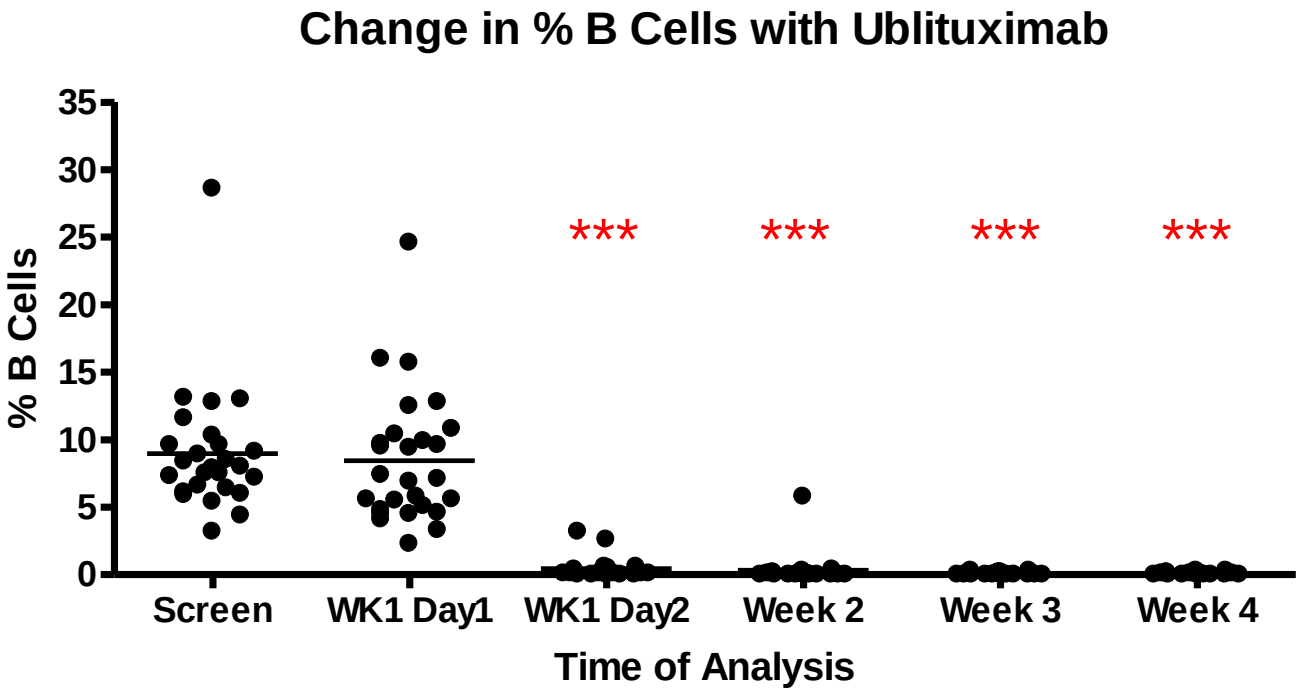

***p<0.001 Bonferroni's Multiple Comparison Test compared to Screening and Day 0

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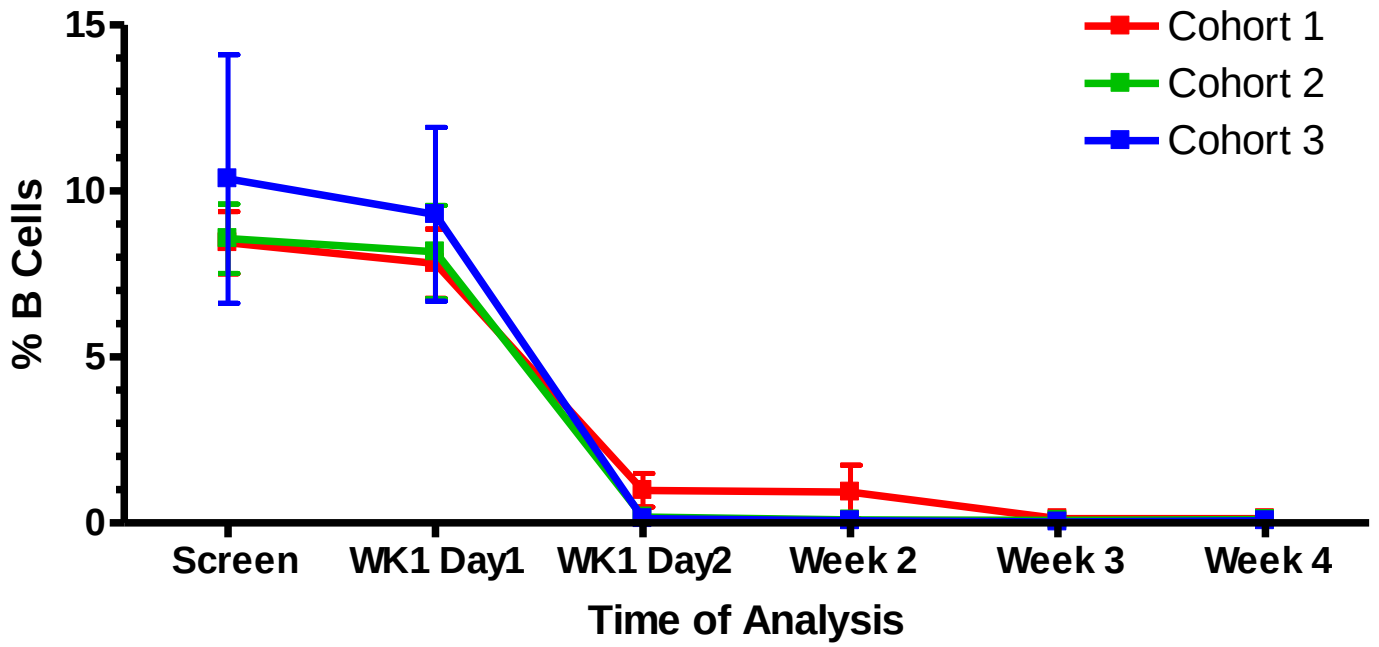

*No statistical difference (ANOVA) between cohorts at each time point.
Error bars are mean±SEM.

All patients received the same total dose of 600 mg, only infusion times differed.

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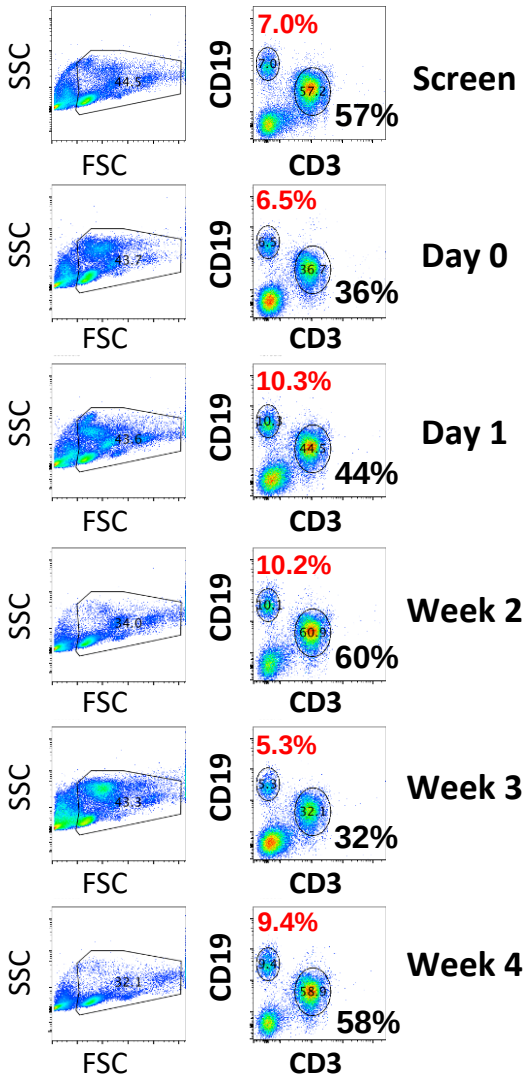
T Cell Analysis

Placebo Phase



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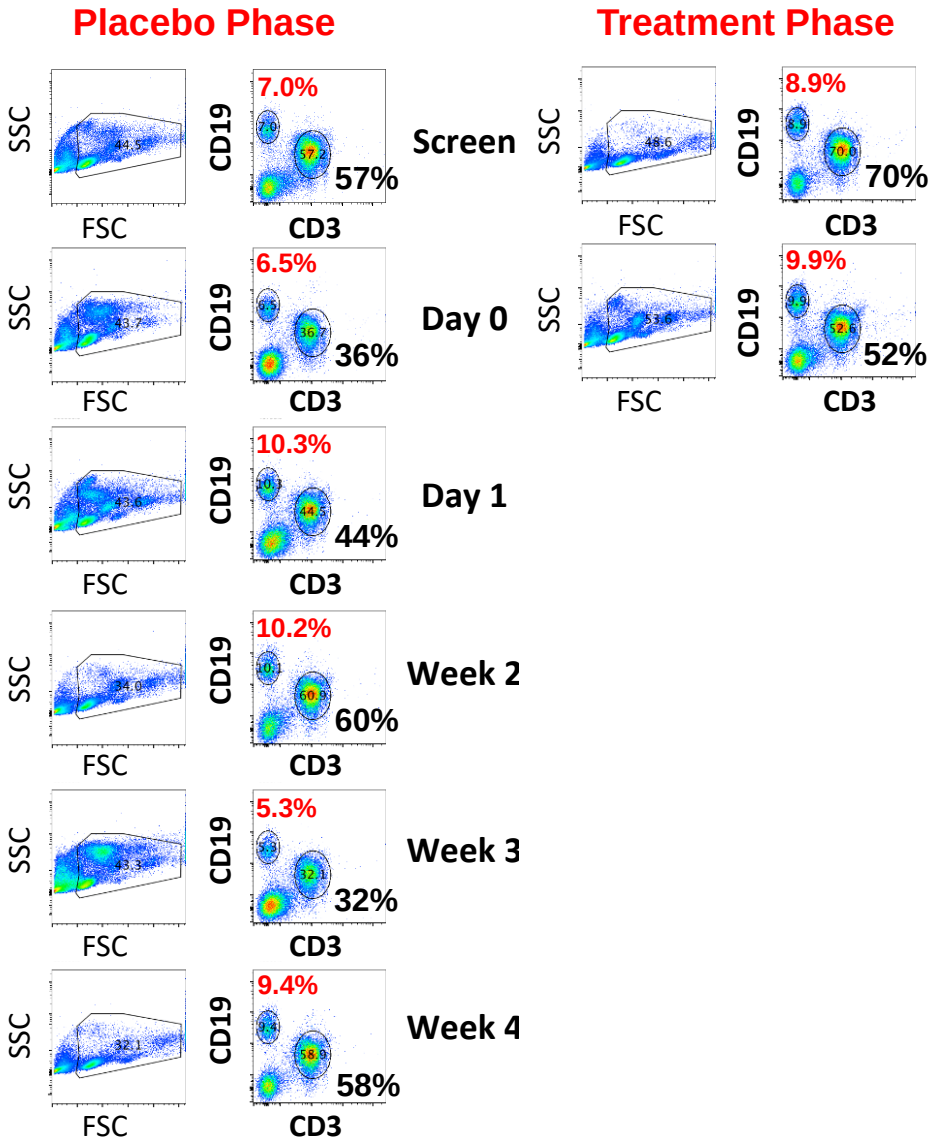

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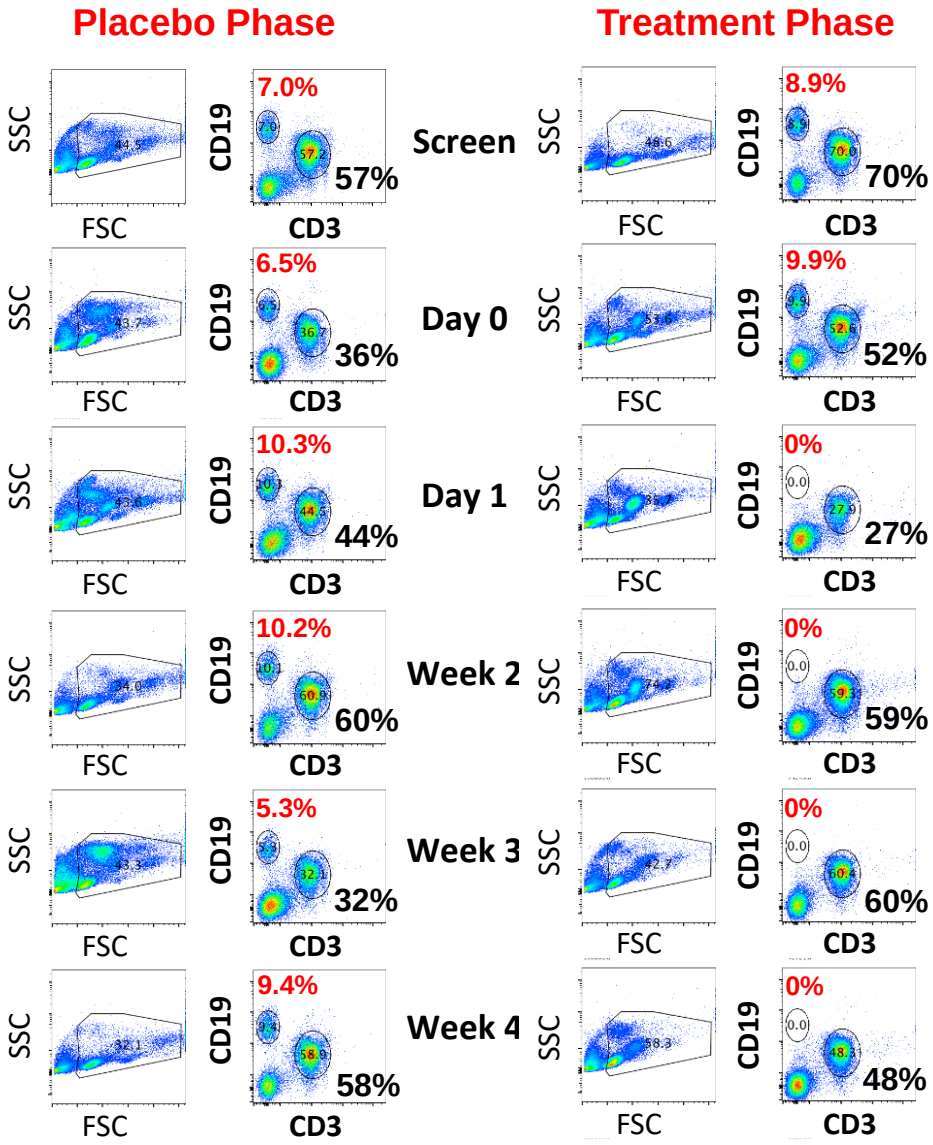

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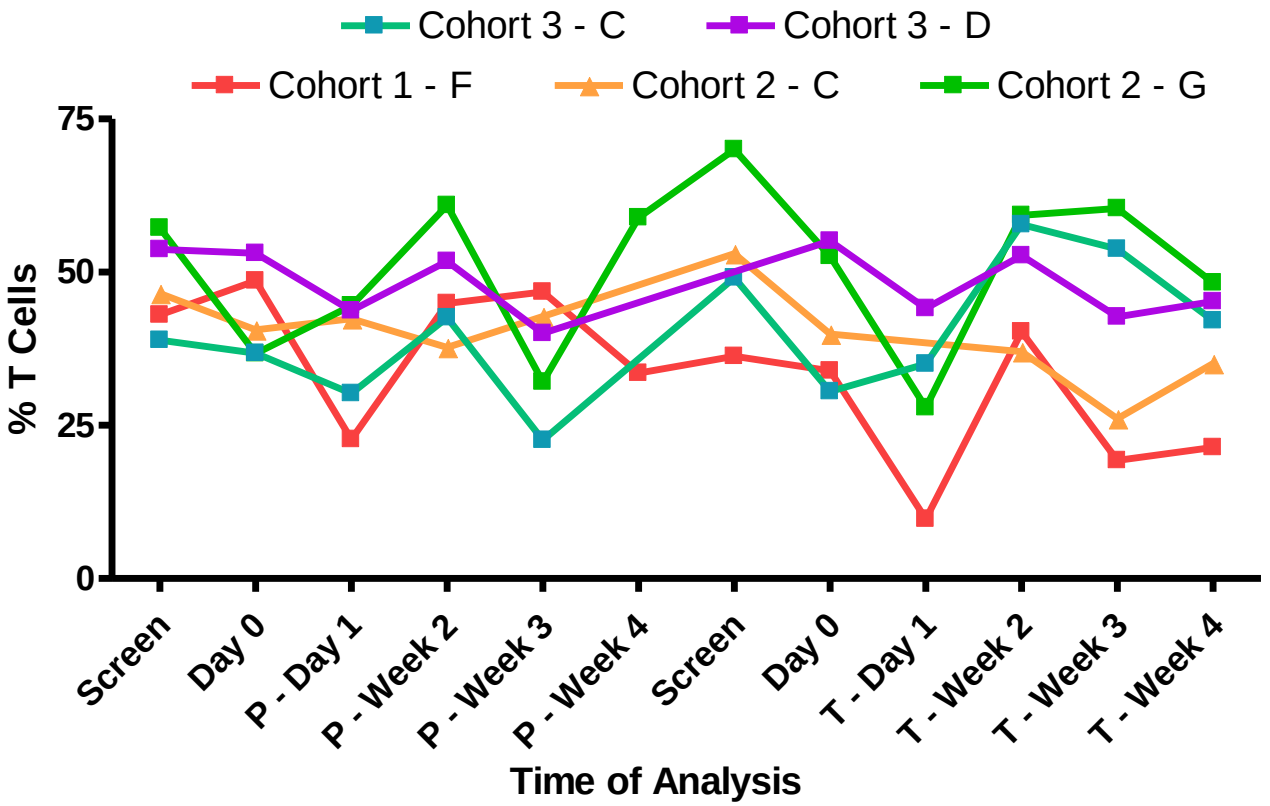

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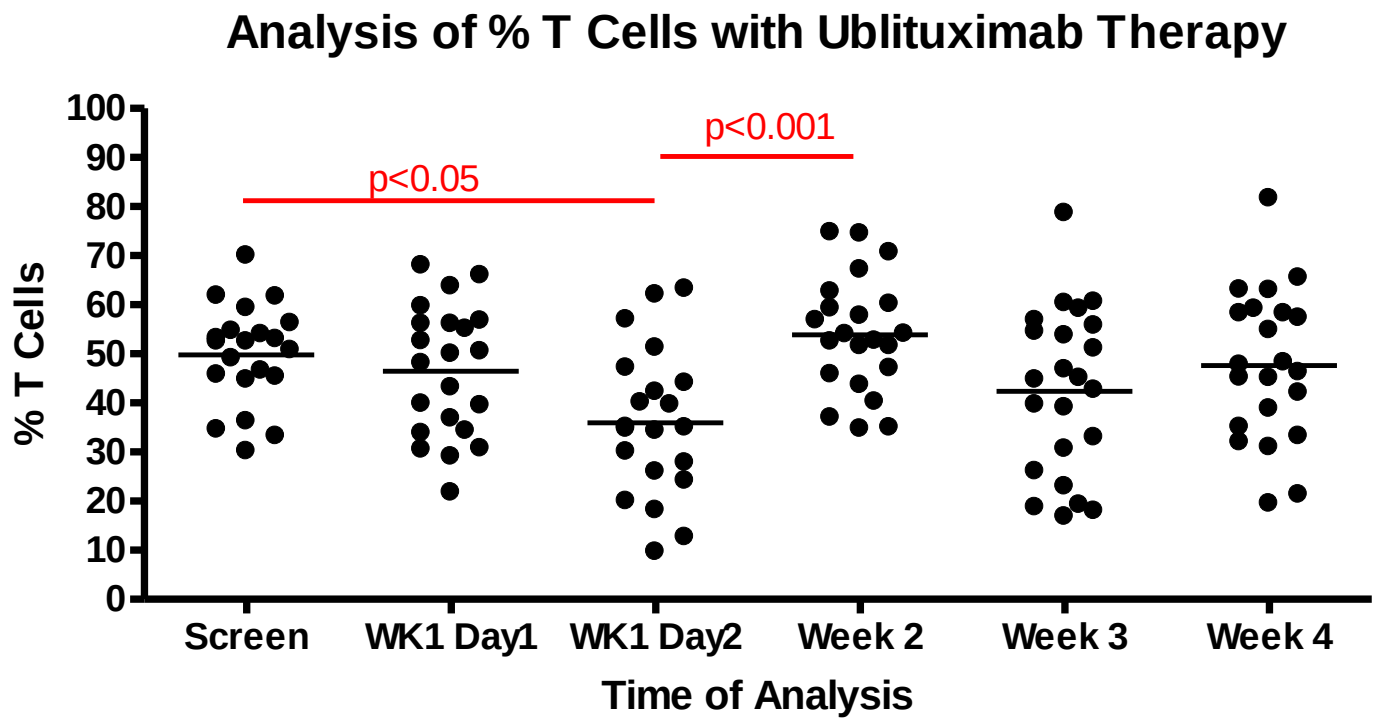

Statistical analysis with Bonferroni's Multiple Comparison Test

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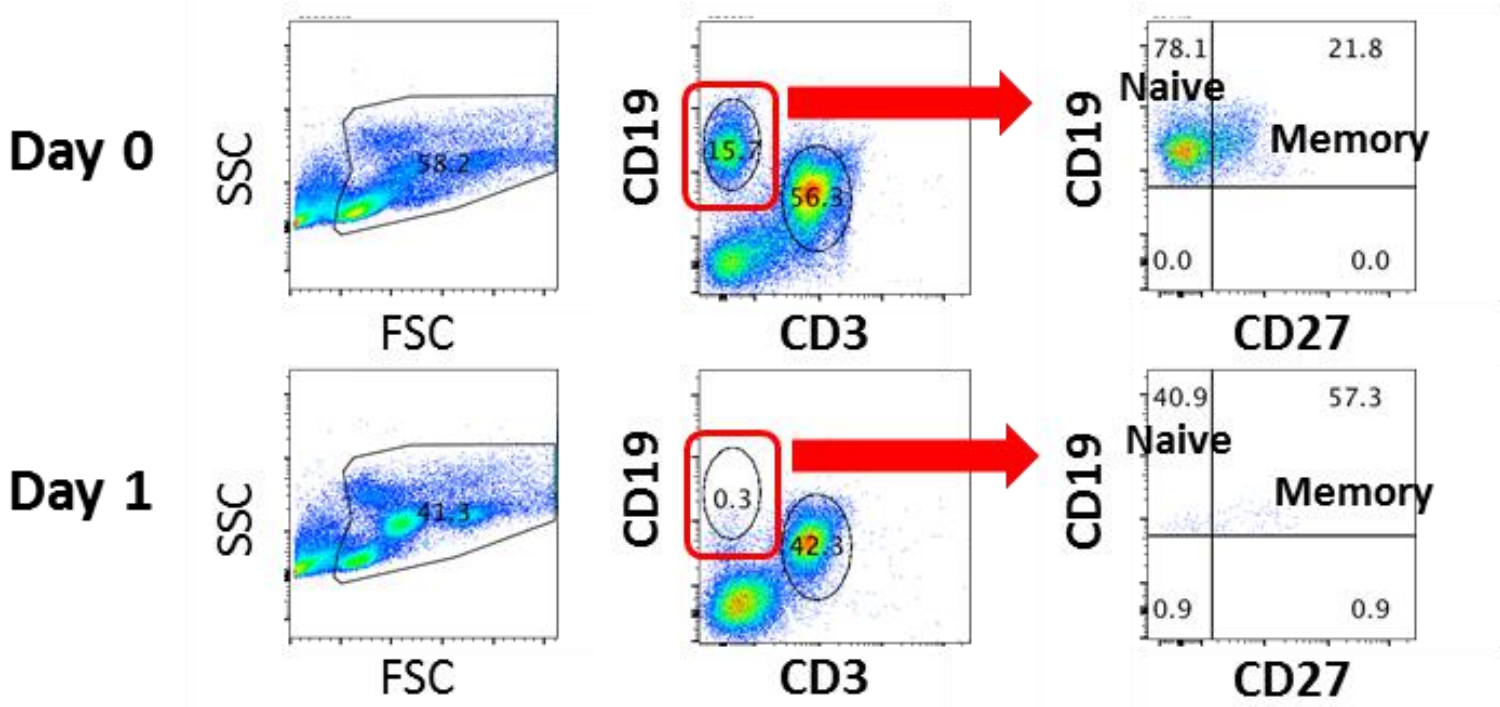
B Cell Subset Analysis



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Summary

- Ublituximab is well-tolerated, with only mild infusion reactions (Grade 1-2) being observed, even with infusion times reduced to 1 hour.
- Ublituximab efficiently depletes B cells (99%), meeting the endpoint of >95% depletion within two weeks of second dose, comparable to ocrelizumab.
- Although there is a transient decrease in T cells after the initial dose of ublituximab, T cell numbers are fairly stable over time.
- Memory B cells seem slightly more resistant to depletion, but are efficiently depleted in all patients.
- A comprehensive analysis of B and T cell profiles is being performed to understand how B cell depletion influences T cell profiles, and to characterize the B cell repletion.
- This one year study of ublituximab in RMS patients is ongoing and clinical and MRI measures will be reported at future congresses.

Acknowledgements

Ohio State University, Columbus, OH
Michael K. Racke, MD
Stephanie Scarberry, RN
Yue Liu, MS
Matthew Gormley
Amy Lovett-Racke, PhD

Hope Neurology Multiple Sclerosis Center, Knoxville, TN
Sibyl Wray, MD
Brenda Albertson, CCRP

SC3 Research Group, Pasadena, CA
Richard Shubin, MD
Ngoc Kim Nguyen
Cassie Tran

Associates in Neurology PSC, Lexington, KY
Cary L. Twyman, MD
Laura Sanders, CCRC

Central Texas Neurology Consultants, Round Rock, TX
Edward J. Fox, MD
Lori Mayer, DNP
Koni Lopez

TG Therapeutics, New York, NY
Wendy Su, PhD
James Eubanks, PhD